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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/366,[illegible]	12/29/94	POMERANTZ	APV-022.01

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EXAMINER	
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ART UNIT	PAPER NUMBER
1638	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/366,083	Applicant(s) Pomerantz et al.
	Examiner Terry A. McKelvey	Group Art Unit 1636

X Responsive to communication(s) filed on 3 19 98

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) 1-21, 24, 27-30, 34, 36, and 40-88 is/are pending in the application.

Of the above, claim(s) 1-21, 24, 27-30, 34, and 36 is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

X Claim(s) 40-88 is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

X See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948. (Substitute PTO-948)

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

X Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

Interview Summary, PTO-413

X Notice of Draftsperson's Patent Drawing Review, PTO-948 (Substitute PTO-948)

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. §§ 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. § 1.821(d). The application refers to sequences without the use of the correct identifier.

For example, Figure 1C in the application sets forth sequences without sequence identifiers.

Applicants should carefully review the specification to identify and properly label each sequence that is referred to within the specification, including drawings. Sequences in drawings can be identified with a SEQ ID NO: in the Brief Description of the Drawings for the figure or be present in the figure itself. If one or more sequences are referred to in the specification that are not present in the Sequence Listing, then a new Sequence Listing, a new CRF diskette containing the Sequence Listing and a new statement that the two are the same and includes no new matter must be submitted in order to fully comply with the Sequence Rules.

Applicants are required to comply with all of the requirements of 37 C.F.R. §§ 1.821 through 1.825. *Any* response

to this Office Action which fails to meet *all* of these requirements will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F.R. §§ 1.821 through 1.825 did not preclude the continued examination of the application on the merits, the results of which are communicated below.

Election/Restriction

Applicant's election of Group III, claims 22-23, 25-26, 31-33, 35, and 37-39 (now canceled, replaced with claims 40-88) in Paper No. 12, filed 3/19/98 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-21, 24, 27-30, 34, and 36 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 12.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out the invention.

Claims 42-84 and 81-84 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

With regard to claims 42, 46-47, 51-54 and 81, "variant(s)" of different domains that are set forth in the claim are also claimed. However, the application as filed does not describe variants of these domains in any fashion. The applicant points to specific sections of the specification in support of these newly filed claims. However, a close examination of the cited sections did not reveal the concept of "variants" of the domains.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 41-68, 72-74, and 81-84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With regard to claim 40, the use of "distinct families" renders the claims vague and indefinite because the metes and bounds of what constitutes such families in this context are unclear. There is no clear art-recognized definition of distinct families for DNA binding domains. For example, in the art, there are different types of zinc-finger domains. Do the different types of zinc-finger domains constitute distinct families, or are they the same distinct family? Homeodomains have a helix-turn-helix structure. Are they distinct from helix-turn-helix domains? What differentiates one distinct family from another?

With regard to claim 41, there is no positive antecedent basis for "the nucleic acid binding domain" (there is only a plural in claim 40).

With regard to claims 42, etc, the use of "and variants thereof" renders the claims vague and indefinite because the metes and bounds of what constitutes "variants" in this context are unclear and there is no clear art-recognized definition. I.e. "variants" encompass any mutated domains mutated in any

fashion and thus would read on any protein domain, or does it include only those which retain the same function? There is no clear art-recognized definition for this term and the specification fails to set forth a definition (or any mention of variants for that matter .

With regard to claim 48, there is no positive antecedent basis for "tne zinc finger domain".

With regard to claim 72, the use of "any one of claims 40" renders the claim vague and indefinite because it implies that there are plural claims, even though only one, claim 40, is recited.

With regard to claim 73, the use of "comprising expression control sequences" renders the claim vague and indefinite because when adding a new component to an earlier product, it should be "further comprising", instead of merely "comprising".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, or

[illegible] one year prior to the date of application for patent in the United States.

Claims 40-43, 51-59, 65-68, and 71-72 are rejected under 35 U.S.C. 102(b) as being anticipated by Brugnera et al (R).

Brugnera et al teach a nucleic acid encoding a chimeric protein comprising a POU-specific DNA-binding domain, an Antp homeodomain, and a third domain (comprising an activation domain from Oct-2 POU, because only the homeodomain part of Oct-2 was replaced) linking the two (Figure 1; throughout the reference). The chimeric protein recognizes both Antp and octomer binding sites, suggesting that each domain contributes to DNA binding specificity (page 361, column 2; page 362, column 2) and thus would bind to a different composite binding site with higher affinity than to the separate binding sites. A vector comprising the nucleic acid is also taught (Materials and Methods section). It is noted that activation domains function by interacting with a cellular component and thus would be encompassed by "domain interacting with a cellular component".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 a which forms the basis for all obviousness rejections set forth in this Office action:

> a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 41-72 are rejected under 35 U.S.C. 103 a as being unpatentable over Park et al (AW2) in view of Mitchel et al S., Harrison T and Schultz U.

Park et al teach a general strategy for designing proteins to recognize specific DNA-binding sites: this strategy is to select segments of proteins, each of which recognizes particular DNA segments and to stitch these segments together via a short peptide with a cysteine crosslink in a way compatible with each peptide being able to bind to its own DNA segment. This technique creates a protein that recognizes the composite site page 9094, column 1). This reference also teaches that use of the Gly-Gly-Cys linker is not essential in the design, that the cysteine can be replaced and a continuous approximately 70 amino-acid protein that should recognize a predictable site can be made page 9095, column 2). The design is not limited to v-Jun. Any protein or other molecule that recognizes a specific DNA sequence by binding along the major groove could be a candidate. Many such cases are now known so that we already have a collection of available partial-binding sites that could be combined to form composite target-binding sites for designing binding proteins. Of course, the segments of these proteins should be designed so that the intramolecular interactions are not so strong as to compete with binding to the DNA (pages 9095-9096).

Park et al do not teach to specifically use the DNA-binding domains from distinct families of nucleic acid binding domains, use of specific types of domains such as zinc-finger domains.

Mitchell et al teach that different DNA binding transcription factors are composed of a surprising variety of usually separable DNA binding and transcriptional activation domains (page 372, column 2). This reference teaches zinc-finger domains, homeodomains, helix-turn-helix domains, steroid hormone receptor domains, leucine zipper domains, etc (pages 372-373). Various types of separable activation domains are also taught: acidic domains that can form an amphipathic alpha-helical structure, glutamine-rich domain, and proline-rich domain (pages 373-375).

Harrison teaches that many DNA-binding proteins recognize specific sites through small, discrete domains and that these domains can be interchanged between proteins, showing that they are independent folded units. Many different DNA-binding domains are taught, including HTH, homeodomains, different types of zinc-finger domains, steroid receptor DA binding domains, etc. Representative proteins having the domains, such as Zif268, etc are also taught and referenced (page 718).

Schultz teaches that enzymes can be created by adding or replacing entire binding or catalytic domains to generate hybrid enzymes with novel specificities. Selective fusion of nucleic acid-specific binding domains may produce sequence-specific DNA or RNA cleaving enzymes (page 431, column 1). This reference teaches that tailor-made enzymes have applications in chemistry, biology and medicine.

It would have been obvious to one of skill in the art at the time the invention was made to use the various DNA binding domains, activation domains, and cleavage domains taught by Mitchell et al, Harrison, and Schultz in the general strategy for designing proteins to recognize specific DNA-binding sites taught by Park et al because Park et al teach that it is within the ordinary skill in the art to stitch the DNA binding domains together from any proteins that recognize a specific DNA sequence by binding along the major groove, to recognize a composite site and Mitchell et al, Harrison, and Schultz teach such domains that can be functionally separated and recombined with other domains. One would have been motivated to do so for the expected benefit of creating a protein that recognizes the composite site, thereby increasing the specificity of the chimeric protein, as taught by Park et al, and creating hybrid enzymes with novel specificities

that have applications in chemistry, biology and medicine as taught by Schultz. Absent evidence to the contrary, there would have been a reasonable expectation of success that the domains taught by Mitchell et al and Harrison could be combined with each other to create a protein that recognizes a composite binding site as taught by Parks et al.

With regard to making a nucleic acid and vector comprising the nucleic acid which encodes the chimeric protein, it would have been obvious to do so because Parks et al teach that a continuous approximately 70 amino-acid protein that should recognize a predictable site can be made, instead of using a cysteine linker, and thus it would have been obvious to make a nucleic acid that encodes this protein and place the nucleic acid in a vector to express the protein, because such a way of making a mutated, recombinant protein is and was well known in the art.

With regard to the use of any specific domain or combinations of domains recited in the claims, it would have been obvious to make any of the recited combinations because the recited domains are all taught in the cited references or are and were well known in the art, and Parks et al teach that any combination of domains can be used.

With regard to the inclusion of an activation domain in the chimeric protein, it would have been obvious to do so because the cited references teach that the activation domain are separate from the DNA binding domains and thus can be included. One would have been motivated to do so for the expected benefit of making a transcriptional activation protein that binds to a more specific composite site, as taught by Parks et al.

With regard to separating the domains by one or more amino acids in the chimeric protein, it would have been obvious to do so because Parks et al teach that the domains can be separated by a linker.

Claims 40-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al (AW2), Mitchel et al (S), Harrison (T) and Schultz (U) as applied to claims 40-72 above, and further in view of Gossen et al (A).

The teachings of Park et al (AW2), Mitchel et al (S), Harrison (T) and Schultz (U) are cited above and applied as before. These references do not specifically teach placing the nucleic acid encoding the chimeric protein into a vector in which the expression of the chimeric protein is under the control of a promiter permitting gene expression in eukarytoic cells, a kit

comprising the nucleic acid encoding the chimeric protein and a gene operably linked to the composite binding site, use of the chimeric protein for modulating expression of a gene in a cell comprising modulating expression of the chimeric protein in a cell which includes a gene operably linked to the composite binding site, and a method of making a cell for use in the claimed expression method.

Gossen et al teach a nucleotide molecule coding for a chimeric transactivator fusion protein comprising a DNA binding domain (tet repressor binding domain) and a transactivation domain (such as VP16 of HSV). A negative system, comprising a repressor domain, is also taught (column 2). A second nucleic acid is taught coding for a heterologous protein which is operably linked to a tet operator (the binding site for the DNA binding domain). A method to regulate gene expression by cultivating the eukaryotic cell comprising the nucleic acid vectors in a medium comprising tet is also taught, as is a kit comprising the nucleic acids (abstract; columns 1-3). A method of making such eukaryotic cells by transfecting the nucleic acids into the cells is taught (columns 3, 9). This reference also teaches that it is desired to create regulatory systems that do not rely on endogenous control elements (column 1 .

It would have been obvious to one of ordinary skill in the art at the time the invention was made to form a transcriptional regulatory system from the DNA encoding a chimeric transactivation protein made obvious by the teachings of Park et al (AM), Mitchel et al (S), Harrison (T) and Schultz (U), using the method taught by Gossen et al because Gossen et al teach that it is within the ordinary skill in the art to make a nucleic acid vector that encodes a chimeric transactivator fusion protein under the control of a promoter active in eukarytoic cells), make a nucleic acid encoding a heterologous protein operably linked to a regulator binding site that the chimeric protein binds to, place the nucleic acids in a eukaryotic cell, regulate the expression of the chimeric protein, thereby regulating expression of the heterologous protein, and the other cited references teach a chimeric fusion transactivator protein that could be used to regulate the expression of genes in a similar fashion as that taught by Gossen et al. One would have been motivated to do so for the expected benefit of making regulatory systems that do not rely on endogenous control elements, the desirability of which is taught by Gossen et al. Absent evidence to the contrary, there would have been a reasonable expectation of success that the chimeric protein encoding DNA taught by the

other cited references could be used to make a new, non-endogenous element regulatory system using the teachings of Bissen et al.

Conclusion

No claims are allowed.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terry A. McElvey whose telephone number is (703) 305-7213. The examiner can normally be reached on Monday through Thursday from about 7:30 AM to about 5:00 PM. A phone message left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached on (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

November 9, 1998